THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 121-8555

Application for Research Grant
(Use extra pages as needed)

Date:
June 14, 1973

1. Principal Investigator (give title and degrees):

H. Fred Downey, Ph.D.
Assistant Professor of Physiology
Director, Cardiovascular Research
Cardiopulmonary Institute

2. Institution & address:

University of Texas Health Science Center at Dallas
5323 Harry Hines Blvd.
Dallas, Texas 75235

3. Department(s) where research will be done or collaboration provided:

Department of Physiology and
Cardiopulmonary Institute

4. Short title of study:

Effects of Tobacco Smoke and Nicotine on Coronary Collateral Blood Flow

5. Proposed starting date: Soon as Possible

6. Estimated time to complete: 2 years

7. Brief description of specific research aims.

A. To determine the effects of
   1. Tobacco smoke and
   2. Nicotine on coronary collateral blood flow following acute or chronic occlusion of a coronary artery.

B. To determine the effects of these agents on the blood flow to other organs in the setting of acute and chronic coronary artery occlusion.

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8. Brief statement of working hypothesis:

Epidemiologic studies have shown that cigarette smoking is associated with increased incidence and mortality rate from coronary artery disease.[4,9,11,12,16] However, little is known about the direct effect of smoking or nicotine on coronary blood flow in ischemic myocardium. Such information is needed because of the large number of smokers who are suffering from regional myocardial ischemia.

Cigarette smoke and nicotine increase cardiac output, heart work, and coronary blood flow in normal experimental animals and man.[1,3,14,19] Partial obstruction of the coronary circulation limits the coronary hyperemic response to the increased metabolic needs of myocardium stimulated by nicotine[6,15,18] and under these conditions, coronary blood flow is distributed non-uniformly across the ischemic myocardium.[15]

No studies have reported the effects of smoking or nicotine on coronary collateral blood flow, although these agents have been shown to decrease ventricular fibrillation threshold in dogs with acute myocardial infarction.[2] However, if coronary arteries are obstructed gradually, collateral vessels develop which are sometimes able to meet minimal requirements of the myocardium in spite of complete obstruction of a major coronary artery.[17]

Continued on 2a

9. Details of experimental design and procedures (append extra pages as necessary)

Experimental Animals. All experiments will be conducted in adult, conditioned mongrel dogs of uniform size (18 to 23 kg). These animals will be examined by a veterinarian and certified free of respiratory diseases and heart worms. They will have been treated for intestinal parasites.

Acute Coronary Occlusion. To retain cardiovascular reflexes and normal cardiovascular dynamics, chloralose anesthesia will be used.[6] The heart will be exposed through a left thoracotomy while respiration with room air is maintained with a Harvard ventilatory pump. Rectal temperature, arterial blood gases, and arterial pH will be monitored and kept within normal limits throughout the experiment. Routinely, aortic, left ventricular blood pressures, electrogram and heart rate will be recorded. Aortic and circumflex coronary artery blood flows will be measured with a dual-channel electromagnetic flowmeter. These flows will provide an index of cardiac output and flow to normal myocardium. The left anterior descending coronary artery (LAD) will be isolated about 2 cm from its origin and ligated according to the two-step procedure of Harris (partial occlusion for 5 min followed by total occlusion).[7] Approximately 80% of the dogs will survive this insult.

Following coronary occlusion, the regional distribution of coronary blood flow will be measured with radioactive microspheres (8-10 μ diameter) administered via a cannula into the left ventricle, where they are well-mixed in the cardiac output.[3] Microspheres reaching the region normally supplied by the LAD will reflect collateral flow, whereas those reaching tissue supplied by the left circumflex coronary artery will reflect normal (control) coronary flow.[2] Normally tissue supplied by the circumflex coronary artery and tissue supplied by the LAD are equally perfused.[2] Microspheres will be administered after occlusion of the LAD and before exposure to smoke or nicotine to provide base-line measurements of collateral flow in each heart. Subsequent injections of differently labeled microspheres will be made after exposure to tobacco smoke or nicotine to determine the distribution of coronary flow under experimental conditions.

Continued on 2c

The physiology and pharmacology of this vital circulation are not well understood, but there is reason to believe that tobacco smoke or nicotine might effect delivery of blood to ischemic myocardium. Collateral flow increases with arterial blood pressure.[5,8,13] Conversely, pronounced dilation of coronary vessels in normal myocardium decreases coronary collateral blood flow.[7,10] Although tobacco smoke and nicotine elevate arterial pressure, they also cause an autoregulatory dilation of the circulation in normal myocardium so that the net effect of these agents on coronary collateral flow must be experimentally determined. Furthermore, collateral coronary flow may be differently affected by tobacco smoke and nicotine if the development of collateral vessels has been stimulated by gradual, chronic occlusion of a major coronary artery.

Vasomotor responses to tobacco smoke or nicotine may alter the distribution of cardiac output. This distribution can be determined concomitantly with measurements of coronary collateral blood flow.

References have been made to the following publications:

1. Bargeron, L. M., D. Ehmke, F. Gonlubol, A. Castellanos, A. Siegel, and R. J. Bing. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation 15: 251-257, 1957.
2. Bellet, Samuel, N. T. DeGuzman, J. B. Kostis, L. Roman, and D. Fleischmann. The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. Am. Heart J. 83: 67-76, 1972.
3. Bellet, S., J. W. West, O. F. Muller, and U. C. Manzoli. Effect of nicotine on the coronary blood flow and related circulatory parameters. Circ. Res. 10: 27-34, 1962.
4. Best, E. W. A Canadian study of smoking and health, Ottawa Department of National Health and Welfare, 1966, p. 137.
5. Corday, E., J. H. Williams, L. deVera, and H. Gold. Effect of systemic blood pressure and vasopressor drugs on coronary blood flow and the electrocardiogram. Am. J. Cardiol. 3: 626-637, 1959.
6. Corsini, G., P. S. Puri, P. V. M. Duran, and R. J. Bing. Effect of nicotine on capillary flow and vascular capacity on the heart in normal dogs and in animals with restricted coronary circulation. J. Pharmacol. Exp. Ther. 163: 353-361, 1968.
7. Downey, H. F., F. A. Bashour, and S. J. Kechejian. Dynamic effects of nitroglycerine on the distribution of coronary blood flow. Circulation 46: III-147, 1972.
8. Downey, H. F., and F. A. Bashour. Effect of perfusion pressure on transmural distribution of coronary collateral blood flow. Physiologist 15: 121, 1972.
9. Doyle, J. T., T. R. Dawber, W. B. Kannel, S. H. Kinch, and H. A. Kahm. The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, N. Y., and Framingham, Mass., studies. J.A.M.A. 190: 886, 1964.

10. Forman, R., E. S. Kirk, J. M. Downey, and E. H. Sonnenblick. Nitroglycerin and heterogeneity of myocardial blood flow. Reduced subendocardial blood flow and ventricular contractile force. J. Clin. Invest. 52: 905-911, 1973.
11. Hammond, E. C. Smoking in relation to the death rates of one million men and women, in Haenszel, W., editor, Epidemiological approaches to the study of cancer and other diseases, Bethesda, United States Public Health Service, National Cancer Institute, Monograph No. 19, January, 1966, pp. 127-204.
12. Kannel, W. B., W. P. Castelli, and P. M. McNamara. The coronary profile: 12-year follow-up in the Framingham study. J. Occup. Med. 9: 611, 1967.
13. Kattus, A. A., and D. E. Gregg. Some determinants of coronary collateral blood flow in the open-chest dog. Circ. Res. 7: 628-642, 1959.
14. Leb, G., F. Derntl, E. Robin, and R. J. Bing. The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog. J. Pharmacol. Exp. Ther. 173(1): 138-144, 1970.
15. Mathes, P., and J. Rival. The effect of nicotine on regional blood flow in the canine heart. Proc. Soc. Exp. Biol. Med. 138: 361-364, 1971.
16. Mulcahy, R., N. J. Hickey, and B. J. Maurer. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36: 577, 1967.
17. Schaper, W. The Collateral Circulation of the Heart. American Elsevier, New York, 1971.
18. Travell, J., S. H. Rinzler, and D. Karp. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Ann. N.Y. Acad. Sci. 90: 290-301, 1960.
19. West, J. W., S. V. Guzmann, and S. Bellet. Cardiac effects of intracoronary arterial injection of nicotine. Circ. Res. 6: 389-395, 1958.

9. Experimental Design - Con't.

In other control experiments, placebo (saline) will be administered instead of nicotine. All other aspects of these experiments will be the same as in those where smoke or nicotine is administered. Data from these experiments will provide new information on any naturally occurring changes in coronary blood flow and its distribution after acute occlusion of a large coronary artery. This data will serve as a basis for evaluating alteration in collateral flow after treatment with either smoke or nicotine.

Inhalation of Tobacco Smoke. A lighted cigarette will be attached to one end of a tube connected to the air inflow port of the respirator.[4] The portion of the inflow drawn through the cigarette will be adjusted so that the cigarette burns in approximately 5 min. Smoke from both regular and filter cigarettes will be studied.

After 5 min of exposure to smoke, differently labeled microspheres will be administered to map the distribution of coronary blood flow. Following this determination, exposure to smoke will be stopped. At various times in different experiments microspheres labelled with a third isotope will be administered to learn if the effects of smoke continue or are quickly reversed.

Nicotine infusion will be started after the base-line measurement of coronary flow distribution. The rate of infusion will initially be 0.20 µg/kg/min for 5 min. Other infusion rates will be used as the investigation progresses to determine a dose-response curve. At 5 min the distribution of coronary flow will again be determined with the microsphere technique. After this determination, the infusion of nicotine will be stopped. Later a third determination of the distribution of coronary flow will be made.

Chronic coronary artery occlusion will be produced by surgically placing an ameroid constrictor around the LAD.[8,9] These devices cause gradual, usually complete, occlusion of the artery over a period of weeks, allowing collateral vessels to develop. In most dogs these vessels supply sufficient coronary blood flow to prevent cardiac mortality and minimize myocardial necrosis. Even when infarcts occur, they are small, and adequate tissue supplied by collateral vessels is available for study.[3]

The dogs will be studied 6 weeks after implantation of the ameroid constrictors. As with the acute experiments, chloralose anesthesia will be used. Cannulae will be placed in the left ventricle for recording pressure and injection of the microspheres and in the femoral artery for collection of reference blood samples.[5] A cannula will be introduced through a carotid artery into the aorta for recording arterial blood pressure. Rectal temperature, arterial blood gases and arterial pH will be monitored and kept within normal limits. ECG and heart rate will be recorded.

9. Experimental Design - Con't.

Coronary flow blood and its distribution will be determined with the microsphere technique. Differently labeled microspheres will be administered before, during, and after exposure to tobacco smoke or nicotine as described for the acute experiments. Two minutes after the final injection of microspheres the hearts will be stopped with saturated KCl iv, the chest opened and the heart excised for tissue sampling. The region of the Ameroid constrictor will be sectioned to determine the degree of narrowing of the coronary artery. Data from hearts with incomplete occlusions will be treated separately.

Measurement of Regional Coronary Blood Flow. Radioactive microspheres of 8-10 μ diameter (3-M Company) will be injected into the left ventricle before and after drug treatment.[3] From there the microspheres are distributed to each tissue according to the fraction of the cardiac output it receives. Microspheres entering the coronary circulation are nearly 100% trapped in the myocardium and thus serve as an effective indicator of regional blood flow. By labeling the microspheres with three different isotopes, determinations of control (pre-treatment) and experimental blood flows (at two intervals post-treatment) can be made in the same heart.[2,5] Since the extent of collateral development varies among dogs it is very helpful for each heart to serve as its own control.

Two minutes after the last injection of microspheres the heart will be excised and frozen for sampling. Tissue samples will be taken from the control, ischemic, and marginal myocardium. Ischemic tissue will be taken from the region normally supplied by the LAD and marginal tissue will be from the edge of the ischemic region. These samples will be divided transmurally into thirds so that the transmural distribution of flow can be determined. The samples will be weighed, and their radioactivities for each isotope determined by scintillation counting in a triple-channel gamma counter. Standard techniques for isotope separation will be utilized and accomplished with our PDP-8 computer.

Regional blood flow will be calculated by relating the radioactivity per gram of tissue with that of reference samples of arterial blood collected at a constant rate for 1 min after each injection of microspheres.[5] This calculation uses the following formula:

$$MBF = \frac{\left(\frac{RBV}{Rcpm}\right) \times Mcpm}{CT \times \text{Tissue weight}}$$

MBF represents flow to a gram of tissue, RBV is the volume of the arterial blood sample collected as described above, Rcpm and Mcpm are the radioactivities of the reference blood sample and tissue

9. Experimental Design - Con't.

sample respectively, and CT is the collection time of the arterial sample (1 min). Two reference samples will be collected simultaneously through two small cannulae of different lengths inserted through the femoral artery into the abdominal aorta. Similar radioactivities in these samples will verify that the microspheres were well mixed in arterial blood.

This procedure for measuring regional coronary flow is basically the same technique used by Hoffman's group.[5] We are aware of the need to limit the number of microspheres injected so as not to alter systemic and coronary hemodynamics. Also, sufficiently large samples will be counted to minimize statistical errors in the counting procedures for determining radioactivities. In the process of determining collateral myocardial flow, tissue samples from other organs will be obtained and their respective flow determined.

We are presently engaged in an investigation of the effects of anti-anginal and anti-arrhythmic agents on coronary collateral flow using the same approach outlined in this proposal.[1] This experience will permit us to proceed most efficiently with the proposed investigation. Also, we are experienced in preparing dogs with chronic coronary occlusions.

References have been made to the following publications:

1. Bashour, F. A., H. F. Downey, S. Kechejian, and R. Underwood. Effects of nitroglycerine on distribution of coronary blood flow following acute coronary occlusion. Clin. Res. 20: 767, 1972.
2. Becker, L. C., N. J. Fortuin, and B. Pitt. Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. Circ. Res. 28: 263-269, 1971.
3. Becker, Lewis C., and Bertram Pitt. Collateral blood flow in conscious dogs with chronic coronary artery occlusion. Am. J. Physiol. 221: 1507-1510, 1971.
4. Bellet, S., N. T. DeGuzman, J. B. Kostis, L. Roman, and D. Fleischmann. The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. Am. Heart J. 83: 67-76, 1972.
5. Buckberg, G., D. Fixler, J. P. Archie, and J. I. E. Hoffman. Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ. Res. 30: 67-81, Jan. 1972.
6. Cox, Robert H. Influence of chloralose anesthesia on cardiovascular function in trained dogs. Am. J. Physiol. 223: 660-667, Sept. 1972.
7. Harris, A. S. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. Circulation 1: 1318-1328, 1950.
8. Schaper, W. The Collateral Circulation of the Heart. American Elsevier, New York, 1971.
9. Vineberg, A., B. Mahanti, and J. Litvak. Experimental gradual coronary artery constriction by ameroid constrictors. Surg. 47: 765-771, 1960.

10. Space and facilities available (when elsewhere than item 2 indicates, state location):

The Cardiopulmonary Institute will provide the salaries of the principal and collaborating investigators. In addition, the Institute will provide adequate research laboratory, office, and animal facilities. Available in the laboratory for use in this investigation will be the following:

1. A six-channel physiological recorder with pressure, ECG, heart rate, and voltage couplers.
2. Micron electromagnetic blood flowmeters.
3. A triple-channel, 100 sample automatic gamma counter with teletype output and a PDP-8E computer for isotope separation analysis and general data processing.
4. Instrumentation laboratory pH and blood gas analyzer.
5. Respirators, perfusion and infusion pump, pressure transducers.
6. The Radiation Safety Section of the University of Texas Health Science Center at Dallas will provide facilities for storage and disposal of radioactive carcasses.

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append).

13. Publications. (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

12. Biographical sketches of investigator and other professional personnel:

H. Fred Downey, Ph.D.

BIRTHPLACE: REDACTED

EDUCATION:

University of Maryland	9/57-6/61	B.S. 6/61	Dairy Science
University of Maryland	9/61-1/64	M.S. 1/64	Dairy Science
University of Illinois	2/64-6/68	Ph.D. 6/68	Physiology and Biophysics

POSITIONS HELD:

University of Maryland - Teaching Assistant, Dairy Science, 9/61 - 1/63
University of Illinois - Teaching Assistant, Physiology and Biophysics, 9/65 - 9/66
University of Illinois - Assistant Professor, Veterinary Physiology and Pharmacology, 7/68 - 1/72
University of Texas Southwestern Medical School - Assistant Professor, Physiology, 2/72 - Present

ACADEMIC AND PROFESSIONAL HONORS:

B.S. With First Honors
Graduate Fellowship, 1961-1962, Alpha Zeta Honorary Fraternity
Research Fellowship, 1963, Oak Ridge Institute of Nuclear Studies
NIH Traineeship in Biophysics, 1964-1965
NIH Predoctoral Fellowship, 1966-1968
Invited Participant in Alfred Benzon Symposium II on Capillary Permeability held in Copenhagen in 1969

PROFESSIONAL SOCIETIES AND RELATED ORGANIZATIONS:

REDACTED REDACTED

12. Biographical sketch of collaborator:

Paul E. Parker, Ph.D.

BIRTHPLACE: REDACTED

EDUCATION:

University of Texas, Austin 9/63-5/64 Major field - Biology

Southern Methodist University, Dallas 9/64-5/67 B.S. - Biology

North Texas State University, Denton 9/67-8/69 M.S. - Physiology

Michigan State University, East Lansing 9/69-10/72 Ph.D. - Physiology

POSITIONS HELD:

North Texas State University - Laboratory Instructor, Biology, 9/67 - 8/69
North Texas State University - Graduate Research Assistant, Biology, 9/68 - 8/69
Michigan State University - Predoctoral Fellow, Physiology, 9/69 - 10/72
Michigan State University - Post-doctoral Fellow, Physiology, 11/72 - Present
University of Texas Southwestern Medical School - Post-doctoral Fellow, Physiology, To be appointed July 1, 1973

ACADEMIC AND PROFESSIONAL HONORS:

NIH Predoctoral Traineeship, September, 1969 to October, 1972.

PROFESSIONAL SOCIETIES AND RELATED ORGANIZATIONS:

REDACTED

13. Publications: Principal Investigator.

1. Downey, H. F., and E. S. Kirk. Coronary Lymph: Specific activities in interstitial fluid during uptake of ^{42}K. Am. J. Physiol. 215: 1177-1182, 1968.

2. Downey, J. M., H. F. Downey, and E. S. Kirk. Effect of myocardial strains on distribution of coronary blood flow in systole. Physiologist 13: 183, 1970.

3. Bashour, F. A., H. F. Downey, S. J. Kechejian, and R. Underwood. Effects of nitroglycerin on distribution of coronary blood flow following acute coronary occlusion. Clin. Res. 20: 767, Oct. 1972.

4. Bashour, F. A., A. Geumei, and H. F. Downey. Coronary vascular response to diphenylhydantoin. Clin. Res. 21: 80, 1973.

5. Downey, H. F., C. A. Bashour, C. S. Rutherford, and F. A. Bashour. Myocardial and total body extractions of radiorubidium. (Submitted for publication to the J. Appl. Physiol.)

Publications of Collaborator:

1. Parker, P. E., D. E. Dobbins, W. J. Weidner, F. J. Haddy, and G. J. Grega. Effects of hemorrhagic, endotoxin, and cathecholamine shocks on canine gracilis muscle vasculature. Proc. Soc. Exp. Biol. Med. 138: 971, 1971.

2. DiSalvo, J., P. E. Parker, J. B. Scott, and F. J. Haddy. Carotid baroreceptor influence on coronary vascular resistance in the anesthetized dog. Am. J. Physiol. 221: 156, 1971.

3. Parker, P., J. Dabney, J. Scott, and F. Haddy. Cardiovascular effects evoked by selective stimulation of the carotid bodies with O_2 and CO_2. Physiologist. 14: 207, 1971.

4. Parker, P., J. Dabney, J. Scott, and F. Haddy. Vascular effects evoked in the kidney and intestine by selective stimulation of the carotid bodies with hypoxia and hypercapnia. Physiologist 15: 234, 1972.

5. Parker, P., I. Ehrhart, and J. Dabney. Vascular responses evoked in the heart and hindpaw by selective stimulation of the carotid bodies with hypoxia and hypercapnia. Fed. Proc. 32(3): 426, March, 1973.

14. First year budget.

A. Salaries (give names or state "to be recruited")	% time	Amount
Professional (give % time of investigator(s) even if no salary requested)		
H. F. Downey, Ph.D.	40	
P. E. Parker, Ph.D.	20	REDACTED
Technicall		
Arthur Williams, B.S. Research Assistant	80	REDACTED
Animal Caretaker	25	
Sub-Total for A		REDACTED

B. Consumable supplies (by major categories)		
Dogs, conditioned	80 @ $30	2,400
Radioactive microspheres		1,650
Maintenance, computer and Gamma counter		500
Miscellaneous Supplies (cannula, chemicals, recorder and computer paper, counting vials, anesthesia, occluders, etc.)		1,000
Sub-Total for B		$ 5,550

C. Other expenses (itemize)	
Travel to meeting of Federation of American Societies for Experimental Biology or American Heart Association	325
Sub-Total for C	$ 325
Running Total of A + B + C	REDACTED

D. Permanent equipment (itemize)		
Blood Flow Transducers	2 @ $265	$ 530
Sub-Totall for D		$ 530
E		1,925
Total request		REDACTED

E. Indirect costs (15% of A+B+C)

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2		5,900	300	None	2,055	$ 15,755
Year 3	---	---	---	---	---	---

JUSTIFICATION OF BUDGET:

Personnel

Technical assistance is required for animal preparation, sample processing and data collection and analysis. The complex nature of the animal preparation, the use of radioactive isotopes, the operation of such instruments as the blood flowmeter, gamma counter, and laboratory computer require the skills and training of a Research Technician. Mr. Williams is presently employed in our laboratory and is familiar with the procedures to be used in this investigation.

Supplies

Radioactive microspheres with diameters between 8 and 10 microns are available on special order from the 3-M Company. The cost is $750 per 1 mc and $825 for 2 mc. We will require two shipments of 2 mc each of three differently labeled microspheres. By combining our orders with orders of Dr. David Fixler of the University of Texas Southwestern Medical School, the cost of the microspheres can be considerably reduced. The amount budgeted, $1,650, should cover the cost of microspheres for this investigation. Although microspheres of larger diameter are available at lower cost, they tend to overestimate subendocardial flow. The greater mass and specific gravity of the larger microspheres appear to prevent them from making sharp turns out of the penetrating arteries and, thus, divert them to the endocardial tissue (Domenech et al., Circulation Res. 25: 581-596, 1969). However, the 8-10 μ microspheres do not exhibit this tendency to overestimate subendocardial flow (Buckberg et al., Circulation Res. 30: 67-81, 1972). Since measurement of the transmural distribution of coronary collateral flow is a vital part of this investigation, we feel justified in requesting the funds necessary to use the most accurate means of making this measurement, the 8-10 μ microspheres.

16. Other sources of financial support.
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Adenosine in Coronary Lymph	American Heart Assoc., Texas Affiliate	$4,000	7/1/72-6/30/73
MI/Anti-Arrhythmic Drugs/Regional Coronary Blood Flow	American Heart Assoc., Texas Affiliate	$7,500	7/1/73-6/30/74
Coronary Collateral Blood Flow	Cardiopulmonary Institute at Methodist Hospital of Dallas	$2,500	1/1/73-12/31/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers):	Amount	Inclusive Dates
Coronary Collateral Hemodynamics and Distribution	NIH		

10035441850

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name H. Fred Downey, Ph.D.

Signature H. Fred Downey Date 6/15/73

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University of Texas Southwestern Medical School

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Responsible officer of institution

Typed Name F. J. Bonte, M.D.

Title Dean

Signature _____ Date _____

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